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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/216,062	12/18/98	GUO	Y 239/102

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HM12/0913

EXAMINER	
DIBRINO,M	
ART UNIT	**PAPER NUMBER**
1644	11

DATE MAILED: 09/13/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/216,062	Guo, Y.
Examiner	**Group Art Unit**
Mariann DiBrino	1644

☒ Responsive to communication(s) filed on *Jul 14, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-4 and 6* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-4 and 6* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*, filed 6/8/99

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's amendment filed 7/14/00 (Paper No. 10) is acknowledged and has been entered.

2. Applicant's election with traverse of Group I (claims 1-4 and 6), and the species of CD28:gp55 bispecific antibody in Paper No. 10 is acknowledged. However, because the Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The search has been extended to cover CD28:gp 55 and CD28:gp115.

Claims 1-4 and 6 are pending and are currently being examined.

3. The reference "AY" crossed out in the Form 1449 filed 6/8/99 has not been considered because it is written in German and a translation has not been provided.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4 and 6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed immunogenic composition comprising an isolated autologous target diseased cell and a bridge molecule capable of stimulating T cell activation comprising one or more binding sites for one or more costimulatory molecules on the surface of T cells.

The instant claims encompass a composition comprising any autologous target diseased cell and any bridge molecule capable of stimulating T cell activation comprising one or more binding sites for one or more costimulatory molecules on the surface of said T cells. There is insufficient disclosure in the specification on said composition.

The specification discloses (on page 7 at lines 15-16) that said binding sites can be directed towards CD28, 4-1BB, CTLA-4 or (on page 7 at lines 6-9) ICAM-1, ICAM-2, ICAM-3, LFA-1, LFA-2, VLA-1 VCAM-1 B7-1, B7-2 and other cell adhesion proteins and other cell surface proteins which can activate T cell costimulatory pathways through T cell surface proteins or (on page 8 at lines 4-6) antigens, fatty acids, lipids, steroids and sugars that can stimulate or costimulate these effector cells' functions to destroy target cells or (on page 8 at lines 6-23) may be the list of CD antigens disclosed therein. The specification further discloses (on page 7 at lines 20-24) that said bridge molecules include, but are not limited to, bispecific monoclonal antibodies, fusion proteins, organic polymers and hybrids of chemical and biochemical materials. The specification discloses bispecific antibodies CD28:gp55, CD28:gp95, CD28:gp115 and CD28:gp210 (figures and Example 2). The specification further discloses CD28:gp55 armed hepa 1-6 (hepatoma tumor cells), EL-4 (lymphoma cells) or SMCC-1 (colon carcinoma cells) (Examples 7, 8). The specification also discloses EL-4 tumor cell armed -Bi-Mab anti-gp115-anti-4-1BB (4-1BB is a glycoprotein expressed on primed T CD4+ and CD8+ T cells) (Example 8).

The specification discloses (on page 7 at lines 25-31 and on page 8 at lines 1-3) that the antigen on the target cell serving as an anchor for the bridge molecule can be any molecule, including but not limited to, proteins, glycoproteins, lipids, glycolipids, phospholipids, lipid aggregates, steroids, and carbohydrate groups such as disaccharides, oligosaccharides and polysaccharides, and further, may be transferrin receptor, LDL receptor, gp55, gp95, gp210, ICAM-1, ICAM-2, collagen and fibronectin receptors, transferrin receptors, Fc receptor and cytokine receptors.

The specification discloses that the tumor cells can include among others brain tumors, pancreatic tumors, lung tumors, colon tumors, liver tumors, breast tumors, gynecologic tumors, prostate tumors, bladder tumors, skin tumors and soft tissue tumors (page 47, lines 14-28).

The specification also discloses human clinical data on human hepatocellular carcinoma and colon cancer (Example 16).

The instant claims encompass bridge molecules that bind to costimulatory molecules other than CD28, 4-1BB and CTLA-4. The instant claims also encompass bridge molecules that are not limited to bispecific monoclonal antibodies and tumor cells that are not limited to hepatocellular carcinoma cells and colon carcinoma cells. There is insufficient disclosure in the specification on said composition and the components of said composition.

6. Claims 1-4 and 6 are rejected under 35 U.S.C. 112, first paragraph, because: 1) the specification, while being enabling for a composition comprising a hep 1-6 tumor cell and anti-CD28 Bi-Mabs comprising gp55, gp 115, gp95 or gp210, or comprising CD28:gp55 armed hepa 1-6 cells, EL-4 cells or SMCC-1 cells, or comprising EL-4 tumor cell armed -Bi-Mab anti-gp115:anti-4-1BB to stimulate T cells, does not reasonably provide enablement for the claimed composition comprising any tumor cell, any bridge molecule comprising one or more binding sites for any one (or more) costimulatory molecules on the surface of a T cell, 2) the specification, while being enabling for a vaccine/composition comprising CD28:gp115 Bi-Mab used for treating human heptatocellular carcinoma and colon cancer, does not reasonably provide enablement for the claimed vaccine comprising any tumor cell, any bridge molecule comprising one or more binding sites for any one (or more) costimulatory molecules on the surface of a T cell for the treatment of any disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims recite a composition comprising a target diseased cell and a bridge molecule comprising one or more binding sites for one or more costimulatory molecules on the surface of T cells. However, the specification fails to disclose any said composition except for a hep 1-6 tumor cell and anti-CD28 Bi-Mabs comprising gp55, gp 115, gp95 or gp210, or comprising CD28:gp55 armed hepa 1-6 cells, EL-4 cells or SMCC-1 cells, or comprising EL-4 tumor cell armed -Bi-Mab anti-gp115:anti-4-1BB.

The specification discloses (on page 7 at lines 15-16) that said binding sites can be directed towards CD28, 4-1BB, CTLA-4 or (on page 7 at lines 6-9) ICAM-1, ICAM-2, ICAM-3, LFA-1, LFA-2, VLA-1 VCAM-1 B7-1, B7-2 and other cell adhesion proteins and other cell surface proteins which can activate T cell costimulatory pathways through T cell surface proteins or (on page 8 at lines 4-6) antigens, fatty acids, lipids, steroids and sugars that can stimulate or costimulate these effector cells' functions to destroy target cells or (on page 8 at lines 6-23) may be the list of CD antigens disclosed therein. The specification further discloses (on page 7 at lines 20-24) that said bridge molecules include, but are not limited to, bispecific monoclonal antibodies, fusion proteins, organic polymers and hybrids of chemical and biochemical materials. The specification discloses bispecific antibodies CD28:gp55, CD28:gp95, CD28:gp115 and CD28:gp210 (figures and Example 2). The specification further discloses CD28:gp55 armed hepa 1-6 (hepatoma tumor cells), EL-4 (lymphoma cells) or SMCC-1 (colon carcinoma cells) (Examples 7, 8). The specification also discloses EL-4 tumor cell armed -Bi-Mab anti-gp115:anti-4-1BB (4-1BB is a glycoprotein expressed on primed T CD4+ and CD8+ T cells) (Example 8).

The specification discloses (on page 7 at lines 25-31 and on page 8 at lines 1-3) that the antigen on the target cell serving as an anchor for the bridge molecule can be any molecule, including but not limited to, proteins, glycoproteins, lipids, glycolipids, phosphlipids, lipid aggregates, steroids, and carbohydrate groups such as disaccharides, oligosaccharides and polysaccharides, and further, may be transferrin receptor, LDL receptor, gp55, gp95, gp210, ICAM-1, ICAM-

2, collagen and fibronectin receptors, transferrin receptors, Fc receptor and cytokine receptors.

The specification discloses that the tumor cells can include among others brain tumors, pancreatic tumors, lung tumors, colon tumors, liver tumors, breast tumors, gynecologic tumors, prostate tumors, bladder tumors, skin tumors and soft tissue tumors (page 47, lines 14-28).

The specification also discloses human clinical data on human hepatocellular carcinoma and colon cancer using CD28:gp115 Bi-Mab (Example 16).

The instant claims encompass bridge molecules that bind to costimulatory molecules other than CD28, 4-1BB and CTLA-4. The instant claims also encompass bridge molecules that are not limited to bispecific monoclonal antibodies and tumor cells that are not limited to hepatocellular carcinoma cells and colon carcinoma cells. The instant claims encompass vaccines and compositions comprising any diseased cell, any bridge molecule comprising one or more binding sites for one or more costimulatory molecules on the surface of T cells in a patient mammal for treating any diseased mammal having diseased cells. The specification provides no guidance as to which of the numerous combinations of the disclosed substances can serve as binding sites for costimulatory molecules, or can serve as bridge molecules, and what combinations can be used to "arm" any particular tumor cell. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed compositions can be used as vaccines or for the treatment of any diseased mammal having any diseased cells. Because of this lack of guidance, the extended experimentation that would be required to determine which substances would be suitable components for the claimed composition/vaccine, and the fact that work from a number of laboratories has implicated CD28 as the major costimulatory receptor on T cells (Allison et al, Current Opinion in Immunology, Vol. 7, 1995, pages 682-686, especially Introduction section), and due to the difficulty in predicting whether therapeutic success in relying upon increasing CTL responses for anti-tumor therapy will be achieved even if a significant increase in anti-tumor CTL is obtained by immunization (i.e., loss of expression of tumor antigens or HLA/MHC molecules, especially page 178, column 2, second full paragraph of Boon, Int. J. Cancer, Vol. 54, 177-180, 1993 pages 177-180) it would require undue experimentation for one of skill in the art to arrive at other components for said composition/vaccine and to use said composition/vaccine. The enablement provided by the specification is not commensurate with the scope of the claims.

7. Claims 1-4 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1 and 3 recite the limitation "said patient mammal" in lines 8 and 7, respectively. There is insufficient antecedent basis for this limitation in the claim.

b. Claims 1 and 3 are indefinite in the recitation of "treating said target diseased cell to increase the levels of one or more primary and costimulatory T cell activation molecules" because it is not clear what is being used to treat said target diseased cell in order to increase levels of said T cell activation molecules.

8. Claim 4 is objected to as being an exact duplicate of claim 2.

9. The disclosure is objected to because of the following informality: Claim 4 is objected to as not having a period at the end of said claim.

Appropriate correction is required.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

11. Claims 1-4 and 6 are rejected under 35 U.S.C. 102(a) as being anticipated by Shi et al (Proc. Amer. Assoc. Cancer Res. March 1996, Volume 37, page 480, Abstract No. 3278).

Shi et al teach a composition comprising human liver tumor cells which are treated in vitro with cytokines IFN-γ and TNF and mixed with bispecific monoclonal antibody to CD28, a costimulatory molecule on T cells, and the tumor-specific antigen GP115. Shi et al teach said composition is used to generate tumor-specific CTL in vitro. Shi et al teach said human liver tumor cells have increased expression of Class I MHC molecules, ICAM-1 and B7. The composition taught by Shi et al is present in tissue culture media (e.g., a pharmaceutically acceptable carrier). Shi et al teach a method of preparation of said composition to increase tumor cell immunogenicity, i.e. of human liver cancer cells, comprising providing an autologous target diseased cell, treating said diseased cell to increase the level of a costimulatory molecule and providing a bispecific antibody with specificities directed towards a tumor-specific antigen and a costimulatory molecule on a T cell, i.e., a bridge molecule. Inherent in the process is that the bridge molecule would attach to said target diseased cell since the target diseased cell possesses the antigen recognized by one arm of the bispecific bridge molecule and that said target diseased cell with bispecific bridge molecule attached would be "collected" in an amount to activate autologous TILs or PBLs, since said TILs or

PBLs were indeed activated in said process. Claim 3 is included in the instant rejection because the instant specification discloses "a cellular vaccine that can stimulate T cell activation in vitro or in vivo, which...leads to an effective immune response against diseased cells" (page 4 at lines 3-4).

The reference teachings anticipate the claimed invention.

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claim 6 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 3, 4, 6-10, 6-10, 12, 13 and 66-105 of copending Application No. 08/872,527. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claim recites "pharmaceutically effective amount" whereas the claims of the '527 application do not; however, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have made a pharmaceutically effective amount of an immunogenic composition. In addition, the claims of the '527 application recite a broad range of species of tumor cells, bridge molecules and costimulatory molecules which are encompassed by the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in patented.

14. The lengthy specification has not been checked to the extent necessary to determine the

presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is (703) 308-0061. The examiner can normally be reached Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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September 6, 2000

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